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GROUP 1600

Applicants' attorney wish to thank the Examiner in charge of the application as well as Mr. Dees, the supervisor, for the courtesies extended to him at the interview on June 25, 2002 which was also attended by Dr. Paris, Dr. Burtin and Dr. Delpy at which time the office action was addressed.

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The claims in the application are claims 24, 25, 27 to 30 and 33 to 35, all other claims having been cancelled.

All of the claims were rejected under 35 USC 112, second paragraph, as being indefinite since the Examiner was of the opinion that method claim 34 did not recite any positive steps and questioned the meaning of the term "functional disorders". The Examiner also was of the opinion that the term "hypoestrogenism" was not in the specification.

Applicants respectfully traverse this ground of rejection since the amended claims are believed to clearly define the invention. The expression "hypoestrogenism" objected to by the Examiner has been changed to "estrogen deficiencies" which is in the specification. For the record, the term "hypoestrogenism" does appear twice in the specification. However, it has been removed from the claims. The expression "functional disorders" no longer appears in the claims. In addition, claim 34 has been amended to indicate that the treatment is without any androgenic effect, and no deleterious effects on the blood vessels. Therefore, the claims are believed to comply with 35 USC 112 and withdrawal of this

ground of rejection is requested.

The Examiner dismissed the declaration of record on the basis that there was not a side-by-side comparison and the amounts of compounds compared were different. The Examiner was of the opinion that the profile for nomegestrol was known.

Applicants respectfully deem that the declaration of record is pertinent to the present application since it clearly demonstrates the differences between sequential continuous regimens and nomegestrol and the prior art progestrins. At the interview, Applicants left with the Examiner a copy of an argument to the last grounds of rejection set forth in the office action of April 23, 2002 and the Examiner's attention is directed to page 3 thereof which shows the difference between sequential administration and continuous administration of the two products and it is deemed that the declaration shows that the effects of the two administrations on the main target organs, i.e. endometrium, the breast and the cardiovascular system both by a sequential regimen and a continuous regimen are quite distinct.

All of the claims were rejected under 35 USC 103 as being obvious over the Plunkett et al reissue patent taken in view of the Fraser et al reference. The Examiner was of the opinion that the Plunkett et al patent teaches a continuous method by administration of progesterones and estrogens and concedes that Plunkett et al

does not teach norgestrol acetate. Fraser et al is cited to show the effects of the addition of norgestrol acetate to estrogenic compounds and that the same induced withdrawal bleeding each month and histological, ultra structural and biochemical changes.

Applicants again call the Examiner's attention to the summary left at the interview and particularly with respect to page 7 regarding the Fraser et al reference. As pointed out at the interview, the clinical trial was very short, namely, only for four months and was of an unusually sequential design. Moreover, the effects on the climacteric symptoms were not evaluated and the levels of estrogen given subcutaneously were extremely high, namely, 25, 50 and 75 mg as compared to Applicants' estrogen range of 0.5 to 3 mg and therefore, the dosages and the tests were completely different and non-analogous. There was an unusual estrogenic stimulation which was continuous and very strong and completely different from one woman to another. There were numerous adverse effects and drop outs which were approximately 17%. The metabolic tolerance was not checked. The lowest dosage used was 0.5 mg and Fraser et al concluded that this was too high. Moreover, this dosage fell outside Applicants' claimed range of 1.5 to 3.75 mg of norgestrol acetate. Moreover, there was no interest whatsoever with respect to HRT and therefore, Fraser et al is completely lacking in Applicants' invention.

With respect to the Plunkett et al patent, this is directed to

an entirely different group of progestrins and there is no suggestion at all of nomegestrol acetate which has a unique pharmacological profile and has endometrial effects never described for other progestrins. An animal pharmacological profile of nomac was published approximately one year before the Plunkett et al application was filed and Plunkett et al could have included nomegestrol acetate if he thought it was useful for his purposes which he did not.

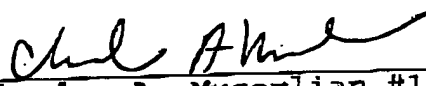
Applicants call attention to the comparison of the unique profile filed with the last response entitled Nomegestrol Profile. As can be seen from the summary (page 10), nomegestrol has a strong progestative activity without any androgenic effect which is contrary to 19-nor-testosterones and MPA both of which were disclosed by Plunkett et al. Moreover, Applicants' compound is without an estrogenic effect which is contrary to 19-nor-testosterones and it also has a strong anti-estrogenic effect which is contrary to the properties of MPA. Moreover, Applicants' compound also has a strong anti-mitotic effect which is contrary to MPA and has perfect metabolic tolerance which is contrary to both 19-nor-testosterones and MPA. Moreover, endometrial effects are inversely dose-related (summary on page 10). At low doses, nomegestrol acetate predominantly induces atrophic endometrium, on the contrary at high doses, nomegestrol acetate predominantly induces secretory endometrium. More importantly, there is no deleterious effect on the blood vessels which is contrary to MPA.

Therefore, it is Applicants' position that Nomagesterol acetate is completely non-analogous to the progesterones taught by Plunkett et al and that the two are not equivalent. Again, the Examiner's attention is directed to page 10 of the brochure left at the interview which compares Applicants' compound with other progesterones and clearly demonstrates Applicants' patentable invention. These dose-related properties are not shared with any other progestin disclosed by Plunkett et al. Therefore, the combination of the prior art would not suggest Applicants' invention since the Fraser et al paper does not teach any interest in HRT and Applicants' compound is not disclosed and is not equivalent to the Plunkett et al progesterones, Applicants wish to call to the Examiner's attention to page 12 thereof. Therefore, the combination of the prior does not teach Applicants' invention and withdrawal of this ground of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable invention. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosure

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MARKED UP VERSION OF CLAIM 34 SHOWING CHANGES MADE

Claim 34 (twice amended). A method of treating [the functional disorders brought about by hypoestrogenism] estrogenic deficiencies in women [and] while further avoiding the appearance of osteoporosis, withdrawal bleeding and cardiovascular diseases in post-menopausal women without any androgenic effect, and no deleterious effects on blood vessels comprising continuously without interruption administering to said women, a combination of 0.5 to 3 mg of an estrogenic compound and 1.5 to 3.75 mg of nomegestrol acetate.